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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,067	MALIK ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1-6,13,14,18 and 24-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-11 and 21-23* is/are rejected.

7)☒ Claim(s) *12,15-17,19 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/15/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Remark

The Group and/or Art Unit location of your application in the PTO has been assigned to Art Unit 1637. All further correspondence regarding this application should be directed to Examiner Young J. Kim whose Group Art Unit is 1637.

Election/Restrictions

Applicant's election with traverse of Group III, claims 7-12, 15-17, and 19-23 in the reply filed on September 9, 2004 is acknowledged. The traversal is on the ground(s) that the searches for at lease groups II and III would be, "either co-extensive or largely overlapping," thus would not constitute an undue search burden (page 1, Response). This is not found persuasive for the following reasons.

MPEP 1893.03, in discussing the prosecution of National Stage application filed under 35 U.S.C. 371, states:

> "Once the national stage application has been taken up by the examiner, prosecution proceeds in the same manner as for a domestic application with the exception that:
> (A) the international filing date is the date keep in mind when searching the prior art; and
> (B) unity of invention proceeds as under 37 CFR 1.475."

37 CFR 1.475 discusses the unity of invention as follows:

> "An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the *requirement of unity of invention shall be fulfilled* ***only when*** there is a technical relationship among those ***inventions involving*** one or more of the same or corresponding ***special technical features***. The expression *"special technical features"* shall mean those technical features that define a contribution which each of the claimed inventions, *considered as a whole,* ***makes over the prior art***.

As already discussed by the previous Examiner in the previous Office Action, the claimed invention lacks unity of invention as the special technical feature does not make over the prior art – i.e., lacks novelty.

The question is not whether the undue search and examination burden is evident, but whether the application has unity of invention, to which the instant application does not.

Applicants do not dispute the prior art cited by the previous Examiner.

Further, Applicants do not traverse the restriction requirement of Groups I, IV, and V. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-6, 18, and 24-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 9, 2004.

Claims 13 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 9, 2004.

Information Disclosure Statement

The IDS received on January 15, 2002 is acknowledged. A signed copy of its PTO-1449 is attached hereto.

Drawings

The drawings received on January 15, 2002 are acceptable.

Claim Objections

Claim 12, 15-17, and 19-20 are objected to for depending on canceled claims.

Claims 12, 15-17, 19, and 20 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim . See MPEP § 608.01(n). Accordingly, the claims 12, 15-17, 19 and 20 have not been further treated on the merits.

Claim 22 is objected to because of the following informalities: claim 22 appears to contain a typographical error. Specifically, in the phrase, "correlating the methylation state of the specific nucleotide sequence or sequences with the presence or absence ***or*** cancer cells in the subject," the underlined word, "or" should be "of."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7-11 are indefinite for the recitation of the phrase, "method of disease **diagnosis** and prognosis in a subject ***diagnosed with a Wilms' tumor cancer***," because while the method

is, in an embodiment, for diagnosing, the subject employed in the method is **already diagnosed** with Wilms' tumor, rendering the claims confusing as to how diagnosis of a disease is done in a subject when said subject is already diagnosed with said disease prior to conducting the method steps. For the purpose of prosecution, the claims are interpreted as being for a method of disease diagnosis and prognosis, wherein said disease is Wilms' tumor.

Claims 7-11 are indefinite for failing to recite a final process step which agrees back with the preamble. While minor details are not required in method/process claims, at least the basic steps must be recited in a positive, active fashion. See *Ex parte Elrich*, 3 USPQ2d, p. 1011 (Bd. Pat App. Int. 1986). For example, claims 7-11 are drawn to a method of disease diagnosis and prognosis of Wilms' tumor cancer, yet the claims recite a final step determining the differentially methylated state of a specific nucleotide sequence or sequences in a subject. The claims do not set forth the conditions/state when the method has been completed [i.e., needs to agree with preamble].

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of disease diagnosis and prognosis in a subject with a Wilms' tumor cancer, wherein said method comprises the determination of the differentially methylated states of a specific nucleotide sequence or sequences in the subject, wherein said specific nucleotide sequence is negative regulatory element or an antisense

regulatory region of WT1 gene, does not reasonably provide enablement for the method wherein said method comprises the determination of the differentially methylated states of **any** nucleotide sequence or sequences of **any** gene in a sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

(A) Quantity of experimentation necessary: The claims require that the method allow the disease diagnosis of Wilms' tumor cancer by determining the methylated state of **any** nucleic acid sequence of **any** gene in a subject. For the skilled artisan to practice the method in commensurate with scope of the claims, said skilled in the art must first identify the genes which are correlated with Wilms' tumor, followed by empirically determining nucleic acids which are correlated with Wilms' tumor when methylated. Empirical determination of identifying genes, followed by testing whether methylation of their sequences are correlated with Wilms' tumor would amount to an undue amount of quantity of experimentation.

(B) Amount of direction or guidance: The specification provides guidance for the diagnosis or prognosis of Wilms' tumor in a subject, wherein said method detects the

methylation status of the nucleotide sequence or sequences of negative regulatory element (NRE) or antisense regulatory region (ARR) of the WT1 gene found on SEQ ID NO: 1.

> "Accordingly, a first aspect of the invention provides a nucleotide sequence encoding a WT1 antisense regulatory region comprising at least a portion of, or consisting of, the sequence shown in SEQ1 [*sic*]" (page 4, 2nd paragraph, specification).
>
> "A third aspect of the invention provides a nucleotide sequence encoding a WT1 antisense regulatory region negative regulatory element (NRE) comprising at least a portion of the sequence shown in SEQ1 [*sic*]". (page 4, 4th paragraph, specification).

While the specification contemplates that the nucleotide sequence, "may be one or more regulatory elements preferably one or more negative regulatory elements (NRE)," the nucleotide sequences involved is disclosed as being either WT1 gene, "or part of the chromosome 11p13 region." (page 5, 2nd paragraph, specification).

The instant specification provides some guidance with respect to conducing the method, wherein the nucleotide sequence is WT1 ARR, for example, the use of *Bsh*1236I, *Spe*I and *Kpn*1 restriction enzymes which cuts at certain C_pG sites with certain methylation state (page 5, bottom paragraph, specification).

However, the specification provides no guidance wherein the method employs **any** nucleotide sequence found on **any** gene for the diagnosis and prognosis of Wilms' tumor.

(C) Absence of working examples: While the instant specification provides some examples pertaining to ARR of WT1 gene, for example, the cloning and characterization of WT1 genomic sequences; diffrential methylation assays involving ARR of WT1 (page 10, specification); PCT-based assay systems for ARR of WT1 (page 11, specification); correlation of the methylation state of the NRE with long term disease prognosis found on ARR of WT1 (page

12, specification), the instant specification lacks further examples that allows a skilled artisan to practice the claimed method for any nucleotide sequence from any genes.

(D) Nature of the Invention: The nature of the invention relates to the diagnosis and prognosis of Wilms' tumor in a sample based on the methylation status of a target nucleic acid.

(E) State of prior art: Vertino et al. (Molecular and Cellular Biology, August 1996, vol. 16, no. 8, pages 4555-4565) discusses the correlation of methylation status in a specific nucleotide sequence for a specific type of cancers, evidencing that empirical experimentation is necessary for diagnosing a specific type of cancer based on a specific nucleotide sequence. Particularly, Vertino et al. discuss the correlation of methylation in *VHL* gene in renal cell carcinomas (page 4555, 1st column, 2nd paragraph), E-cadherin gene in breast and prostate carcinomas (page 4555, 2nd column, 1st paragraph).

(F) Skill level: the skill level of one skilled in the art in question is determined to be high.

(G) Unpredictability of the art: As already discussed, the method of diagnosing a certain disease type, in this case Wilms' tumor, based on the determination of methylation status of any nucleic acid sequence remains unpredictable as empirical determination is needed.

(H) Breadth of the claims: The breadth of claims 7 and 11 embraces a method which allows the diagnosis and prognosis of Wilms' tumor via determining the methylation status of any nucleic acid sequence from any gene.

As the instant specification lacks guidance sufficiently directing a skilled artisan to practice the invention commensurate in scope of the claims, the skilled artisan would be required to conduct empirical experimentation in identifying and correlating the methylation status of all

nucleic acid sequence from every known gene to reasonably determine, if at all, a correlation can be made to Wilms' tumor, amounting to an undue experimentation.

Claims 7-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a method of using a genus of nucleic acids which are different from those disclosed in the specification. The genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID Nos. Thus, applicant has express possession of the WT1 (SEQ ID Numbers 1, 2, and 3) from which ARR and NRE are identified, in a genus which comprises hundreds of millions of different possibilities. Here, no common

element or attributes of the sequences are disclosed, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided. Further, these claims encompass, allelic variants including insertions and mutations. The instant specification acquiesces this fact:

> "The WT1 ARR characterized and utilized as the basis of the invention ***is structurally and functionally distinct from previously described WT1 gene sequences (for example, Call et al, (1994), US patent 5,350,840***" (page 3, bottom paragraph, specification).

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the ARR and NRE of WT1 gene lack any specific structure, is precisely the situation of ***naming*** a type of material which is generally known to likely exist, but, except for those identified by their SEQ ID Numbers, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claims.

In Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed by their SEQ ID Numbers. Therefore, the claims fail to meet the written description requirement by encompassing using nucleic acid sequences which are not described in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Nelson et al. (U.S. Patent No. 5,552,277, issued September 3, 1996).

Nelson et al. disclose a method of detecting cancer (Abstract), said method involving the steps of detecting the hypermethylation of GSTP1 promoter in prostatic tissue sample, wherein hypermethylation indicates the sample is cancerous (or cell proliferative disorder) (column 2, lines 20-28).

Therefore, Nelson et al. anticipate the invention as claimed.

Claims 7 and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Duffy (U.S. Patent No. 5,871,917, issued February 16, 1999).

Duffy discloses a method of detecting hypermethylation and hypomethylation in samples, wherein said method employs tumorous samples, such as Wilms' tumor (claim 1 and 6).

Duffy discloses that tumor cells are differentially methylated from that of the normal cells (Abstract; column 8, lines 45-67; column 20, lines 49-63).

Therefore, Duffy anticipates the invention as claimed.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner can normally be reached from 8:30 a.m. to 6:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a

general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
11/24/04

YOUNG J. KIM
PATENT EXAMINER

yjk